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α-Hydroxymethylation of conjugated nitroalkenes via the Morita–Baylis–Hillman reaction

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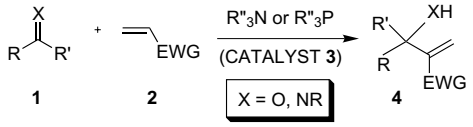
Dedicated to Professor Alfred Hassner on the occasion of his 73rd birthday

Abstract—The Morita–Baylis–Hillman reaction (MBHR) of conjugated nitroalkenes has been successfully carried out for the first time. A variety of aromatic and heteroaromatic nitroalkenes react with formaldehyde at room temperature in the presence of stoichiometric amounts of imidazole and catalytic amounts of anthranilic acid in THF providing moderate to good yields of the multifunctional adducts in most of the cases.

The tertiary amine catalyzed α-hydroxyalkylation or α-aminoalkylation of activated olefins, commonly known as the Baylis–Hillman reaction (see Scheme 1),[1] is an elegant synthetic methodology (such reactions catalyzed by tertiary phosphines were reported by Morita et al.)[2] not only in terms of its simplicity, economy and atom efficiency but also for the fact that the products contain multiple functionalities amenable for further manipulation.[3] The reaction involves the initial Michael addition of the catalyst, a Lewis base **3** (e.g., DABCO), to an activated olefin **2**, followed by trapping of the enolate using an electrophile **1** and β-elimination of the Lewis base **3** yielding an α-methyleno compound **4**. The activated olefins employed thus far are α,β-unsaturated aldehydes,[4] ketones,[5] esters,[6] nitriles,[7] amides,[8] sulfoxides,[9] sulfones,[10] sulfonates[11] and phosphonates.[12] Aldehydes as well as activated ketones and imines are the commonly used electrophiles.[3] Although several tertiary amines can be employed, DABCO has been the catalyst of choice until recently.[3]



Scheme 1.

Although recent years have witnessed an upsurge of activities vis-à-vis the Morita–Baylis–Hillman reaction (MBHR), which include reactions involving novel substrates and catalysts, intramolecular variants, and a variety of applications of the MBH strategy and products in organic synthesis,[3,13] several glaring disadvantages associated with the MBHR still curtail its scope and applicability. Some of them are: (1) the reaction is very slow under normal conditions;[14] (2) β-substituted activated olefins do not react or react only sluggishly;[15] (3) some activated olefins do not normally react or provide only undesired products. For instance, an olefin activated by a nitro group is conspicuous by its absence from the host of activated olefins that have been employed so far in the MBHR.[16] This is despite the fact that conjugated nitroalkenes[17] are excellent Michael acceptors and the first step in the MBHR is the Michael addition of the catalyst. Some of the difficulties that might have been encountered during attempts to use conjugated nitroalkenes as activated olefins might be: (1) instant reversibility of the initial conjugate addition of the tertiary amine catalyst;[18] (2) poor nucleophilicity of

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the nitronate; (3) Michael addition of the nitronate to another molecule of nitroalkene and its propagation leading to oligomers or polymers[19] and (4) polymerization of the nitroalkene per se. Therefore, the MBHR of nitroalkenes is indeed a challenging task.

The MBH products arising from conjugated nitroalkenes are distinguished by the proximal disposition of a double bond, a nitro group and a hydroxy group offering a convenient entry into a variety of useful synthetic intermediates and targets, which would arise from the reactivity of these functional groups individually or collectively. For instance, since the MBH products are still conjugated nitroalkenes, they could perform well as Michael acceptors and Diels–Alder dienophiles. The MBH products can also be regarded as trisubstituted activated alkenes and electron deficient allylic alcohols. While the hydroxymethyl moiety could be easily transformed to ethers, alkyl halides, aldehydes, carboxylates, etc., the nitro group, by virtue of its versatile reactivity, is amenable for the preparation of oximes, hydroxylamines and amines, to name a few.

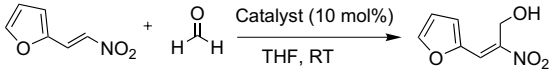
Our preliminary experiments using DABCO as the catalyst were not promising. For instance, attempted MBHR of nitrovinyl furan **5** with 38% aqueous formaldehyde **6** in the presence of 10 mol% of DABCO as the catalyst provided no isolable amounts of the MBH products (Table 1, entry 1). Attempts to use other Lewis bases such as DBU, Et_3N, pyridine, Me_2S, Ph_3P, $(Cy)_3P$ and $(n\text{-}Bu)_3P$ as catalysts in the MBHR of nitroalkenes with formaldehyde also met with failure (entries 2–4 and 8–11). Although DMAP and *N*-methylimidazole provided isolable amounts of the MBH product **7** when nitrovinyl furan **5** was treated with aqueous (38%) formaldehyde **6** in THF (entries 5 and 7),[20] respectable yields were obtained only when imidazole was used as the catalyst (entry 6).[21]

Further experiments using nitrovinyl furan **5** and formaldehyde **6** as the substrates showed that in the presence of catalytic amounts of imidazole (up to 50 mol%, Table 2, entries 1–3), the reaction remains incomplete even after 5 days. However, in the presence of stoichiometric amounts of imidazole, although the improvement in the yield is marginal, the reaction time is reduced to less than a day (20 h, Table 2, entry 4).

Subsequently, additives such as proline,[22] 2-aminophenol and anthranilic acid were screened for their co-catalytic activity in THF and other polar solvents such as DMF, MeOH, CH_3CN and 1,4-dioxane (Table 3). These experiments revealed that (1) in the absence of additives, DMF was the best solvent in terms of the reaction time and % yield (62%, 18 h, entry DMF, Column a); (2) proline did not have any co-catalytic activity as the yields in the presence of 10 mol% of proline were the lowest in all the solvents (Column b); (3) in general, 2-aminophenol had only a marginal influence on the yield in all the solvents (Column c); (4) anthranilic acid exhibited good co-catalytic activity when THF was used as the solvent (71%, 24 h, entry THF, Column d).

In view of the above, THF was used as the solvent in subsequent reactions. It was noticed that 10–20%

Table 1. The Morita–Baylis–Hillman reaction of nitrovinyl furan **5** with formaldehyde **6** in the presence of 10 mol% of various catalysts[a]

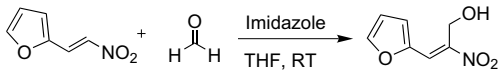


5 **6** **7**

Entry	Catalyst	Time	Yield (%)[b]
1	DABCO	7 d	None
2	DBU	7 d	None
3	Et_3N	7 d	None
4	Pyridine	7 d	None
5	DMAP	5 d	9
6	Imidazole	5 d	40
7	*N*-Methylimidazole	5 d	14
8	Me_2S	7 d	None
9	Ph_3P	7 d	None
10	$(Cy)_3P$	7 d	None
11	$(n\text{-}Bu)_3P$	7 d	None

[a] 38% Aqueous HCHO (excess):THF = 1:1.
[b] Isolated yield after column chromatography.

Table 2. The Morita–Baylis–Hillman reaction of nitrovinyl furan **5** with formaldehyde **6** in the presence of imidazole[a]

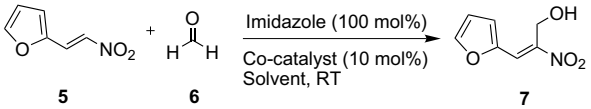


5 **6** **7**

Entry	Imidazole (mol%)	Time (h)	Yield (%)[b]
1	10	120	40[c]
2	20	120	40[c]
3	50	120	42[c]
4	100	20	48

[a] 38% Aqueous HCHO (excess):THF = 1:1.
[b] Isolated yield after column chromatography.
[c] Reaction incomplete.

Table 3. The Morita–Baylis–Hillman reaction of nitrovinyl furan **5** with formaldehyde **6** in various solvents in the presence of imidazole (100 mol%) and 10 mol% of various additives[a]



5 **6** **7**

Solvent entry	Additives, product yield (%),[b] time (h)			
	None (a)	Proline (b)	2-AMP[c] (c)	AA[d] (d)
THF	48 (20 h)	26 (96 h)	40 (60 h)	71 (24 h)
DMF	62 (18 h)	36 (18 h)	56 (24 h)	51 (30 h)
MeOH	48 (30 h)	30 (20 h)	51 (30 h)	50 (50 h)
CH_3CN	48 (20 h)	24 (20 h)	52 (24 h)	51 (30 h)
1,4-D[e]	53 (120 h)	24 (50 h)	63 (45 h)	59 (75 h)

[a] 38% Aqueous HCHO (excess):solvent = 1:1.
[b] Isolated yield after column chromatography.
[c] 2-Aminophenol.
[d] Anthranilic acid.
[e] 1,4-Dioxane.

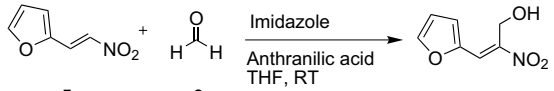
anthranilic acid was the optimum amount of co-catalyst needed and lowering or raising the amount of anthranilic acid had a negative effect on the yield (Table 4, entries 1–5). Similarly, entries 6–8 (Table 4) show that sub-stoichiometric amounts of imidazole were insufficient even in the presence of the co-catalyst anthranilic acid. Longer reaction times and lower yields were encountered under these conditions. Therefore, it appeared most economical to use catalytic amounts (10 mol%) of anthranilic acid in conjunction with stoichiometric amounts of imidazole.

Under the above optimized conditions, a variety of heteroaromatic nitroalkenes (Table 5, entries 1–3) and nitrostyrenes (entries 4–10), including the parent nitrostyrene (entry 10), provided moderate to good yields of the MBH products.[23]

The co-catalytic behaviour of anthranilic acid was further confirmed by the fact that when aniline and benzoic acid were used as additives, the yields were 41% and 44%, respectively (Table 6, entries 2–3). This is attributable to an organocatalytic templating effect[24] of anthranilic acid involving hydrogen bonding[25] with the nitro group and in situ formation of an imine[22] with the aldehyde electrophile.

In summary, conjugated aromatic and heteroaromatic nitroalkenes react with formaldehyde under imidazole mediated conditions in polar solvents at room temperature to provide novel multifunctional molecules. The best yields were obtained when the reactions were carried out in THF at room temperature in the presence of catalytic amounts of anthranilic acid. Future efforts will be directed towards expanding the scope of this reaction by employing aliphatic nitroalkenes, including nitroethylene, as well as electrophiles other than formaldehyde.

Table 4. The Morita–Baylis Hillman reaction of nitrovinyl furan **5** with formaldehyde **6** in THF in the presence of varying amounts of imidazole and anthranilic acid[a]

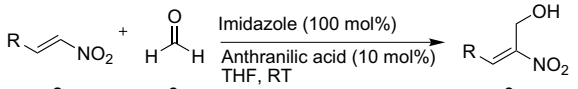


5 **6** **7**

Entry	Imidazole (mol%)	Anthranilic acid (mol%)	Time (h)	Yield (%)[b]
1	100	1	36	61
2	100	5	36	64
3	100	10	24	71
4	100	20	36	74
5	100	50	60	50
6	50	10	48	59
7	20	10	120	47
8	10	10	120	33

[a] 38% Aqueous HCHO (excess):THF = 1:1.
[b] Isolated yield after column chromatography.

Table 5. The Morita–Baylis Hillman reaction of β-substituted nitroalkenes with formaldehyde in the presence of 100 mol% (1 equiv) of imidazole and 10 mol% of anthranilic acid in THF[a]

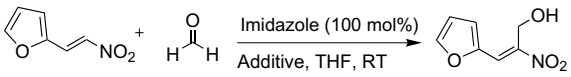


8 **6** **9**

Entry	8,9	R	Time (h)	Yield (%)[b] of **9**
1	**a**	2-Thiophenyl	15	56
2	**b**	3-Furyl	30	40
3	**c**	3-Thiophenyl	30	35
4	**d**	4-MeO–C_6H_4	15	50
5	**e**	2-NO_2–C_6H_3	16	55
6	**f**	3,4-$(MeO)_2$–Ph	36	46
7	**g**	3-MeO–4-OH–Ph	24	60
8	**h**	3,4-(-OCH_2O)Ph	120	63
9	**i**	4-F–C_6H_4	30	25
10	**j**	Ph	24	50

[a] 38% Aqueous HCHO (excess):THF = 1:1.
[b] Isolated yield after column chromatography.

Table 6. The co-catalytic activity of anthranilic acid in the Morita–Baylis–Hillman reaction of nitroalkenes[a]



5 **6** **7**

Entry	Additive (10 mol%)	Time (h)	Yield (%)[b]
1	Anthranilic acid	24	71
2	Aniline	90	41
3	Benzoic Acid	72	44

[a] 38% Aqueous HCHO (excess):THF = 1:1.
[b] Isolated yield after column chromatography.

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14. Many recent reports circumvent this problem via application of reactive activated alkenes, reactive electrophiles, substrates or catalysts possessing hydrogen bonding groups, microwave irradiation, use of excess catalyst, polar (aqueous) medium, high pressure, etc. See Ref. 3a.
15. For instance, crotononitrile, crotonic acid esters, phenylvinyl sulfoxide, etc., require high pressure in order to undergo the MBHR. See Ref. 3a.
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22. For proline co-catalyzed MBHR, see Ref. 21b,c.
23. All the products provided satisfactory IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. General procedure: To a stirred solution of nitroalkene (1 mmol) in THF (2 mL) at room temperature was added imidazole (68 mg, 1 equiv) followed by anthranilic acid (14 mg, 10 mol%). 38% Aqueous formaldehyde **6** (2 mL, excess) was then added and the reaction mixture was stirred at room temperature for the period specified in Table 5. After completion of the reaction (confirmed by TLC analysis), the reaction mixture was acidified with 5 N HCl (5 mL) and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with EtOAc–pet. ether (0–25%, gradient elution) to afford pure **7** or **9**. Characterization data for **7**: Yellow crystalline solid; yield: 71%; mp 87–89 °C (CH_2Cl_2–pet. ether 1:3); IR (KBr) cm^{-1} 3434 (br s), 1651 (s), 1519 (s), 1315 (s), 1025 (s), 742 (s); ^{1}H NMR ($CDCl_3$): δ 2.48 (br s, 1H), 5.04 (s, 2H), 6.62 (dd, $J = 3.3$ Hz, $J = 1.8$ Hz, 1H), 6.99 (d, $J = 3.3$ Hz, 1H), 7.70 (d, $J = 1.8$ Hz, 1H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 56.7 (t), 113.3 (d), 122.1 (d), 122.7 (d), 145.7 (s), 146.9 (s), 147.6 (d); MS (DCI, CH_4) m/e (rel. intensity) 169 (M^+, 100), 153 (38), 147 (36), 133 (11); HRMS (DCI, CH_4) calcd for $C_7H_7NO_4$ (M^+, 100) 169.0375, found: 169.0381.
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